II. SCIENTIFIC SUMMARY

Gaucher disease is the most common lysosomal storage disorder. It is due to an inborn error of glycosphingolipid metabolism resulting from mutations in the gene coding for glucocerebrosidase (GC) (E.C. 3.2.1.45). The GC gene has been mapped to chromosome 1q21. More than 20 different mutations have been described in the human GC gene. Two common mutations account for 80% of the mutant alleles. A correlation between the genotype and clinical phenotype permits separation of the rare neurodegenerative cases from the more common non-neuronopathic disease. The latter, Type 1 disease, occurs commonly among Ashkenazi Jews where it is the most prevalent inherited disorder. Type I disease accounts for 90% of the clinical cases of Gaucher disease. All patients with Gaucher disease have clinical complications frequently leading to discomfort and disability. Complications include hepatosplenomegaly, hypersplenism, anemia, thrombocytopenia and degenerative changes in the skeleton. Many patients have aggressive disease with clinical presentation early in life marked by profound organomegaly, bleeding diatheses, liver failure, esophageal varices, pulmonary compromise, pathologic fractures, bone deformity, and an early death.

There is a need for new forms of therapy to correct this genetic defect. Current treatments are either unavailable or prohibitively expensive. The objective of this proposal is to evaluate gene therapy for Type 1 Gaucher disease. We propose to perform autologous bone marrow transplantation with $CD34^+$ cells transduced by the normal human GC gene. Preclinical data in the mouse model of bone marrow transplantation provides evidence of efficient transduction of bone marrow stem cells and long term expression of the human gene in their progeny. Expression of the transferred human GC gene in macrophages derived from the bone marrow of these animals endures for the life of the mice and is about 4 times the endogenous activity. In Gaucher disease, storage of the undegraded lipid occurs only in this cell type and the pathology of the disorder is mediated by macrophages. Preclinical studies with macrophages from Gaucher patients indicate that transduction of human Gaucher macrophages in culture is sufficient to correct their activity to within the normal range. These results suggest that gene transfer and expression of the GC enzyme in human macrophages is feasible. We have provided evidence that enzymatically competent macrophages are sufficient to treat the disease by either allogeneic transplantation of normal bone marrow or direct correction of macrophage enzymatic activity. We propose to genetically correct $CD34^+$ cells capable of reconstituting the whole BM including MØ. Transfer of the GC gene to $CD34^+$ cells obtained from blood of a Gaucher patient demonstrates a transduction efficiency of approximately 20% and expression of enzyme activity to 20-40 times the amount of activity in enzyme deficient cells.

We will transduce $CD34^+$ cells obtained from the blood of Gaucher patients using a replication defective retroviral vector called R-GC. The vector carries the human GC cDNA. Five (5) patients will be studied over the first year of the study. Patients will be transplanted with autologous $CD34^+$ cells that have been genetically corrected. The transplanted patient will be assessed for the carriage and expression of the transduced gene in peripheral blood leukocytes. GC activity will be used to quantify the extent of restoration of enzyme in these cells. The criteria of clinical responsiveness will be the ability to withdraw enzyme following the transplantation of patients previously treated with enzyme or clinical reversal of symptoms in the patient not receiving enzyme. Clinical parameters to be followed include organ size, hemoglobin/hematocrit, platelet count, plasma angio-tensin converting enzyme concentration, serum non-tartrate inhibitable acid phosphatase, bone marrow morphology and bone structure by x-rays and scans.